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(54) Title: DIAGNOSIS OF CHRONIC REJECTION

(57) Abstract: Methods are disclosed for, early diagnosing chronic rejection (CR) in a transplanted subject, monitoring CR in a transplanted subject at risk of developing CR, preventing, inhibiting, reducing or treating CR in a transplanted subject, or identifying agents for use in the prevention, inhibition, reduction or treatment of CR, based on genes which are differentially expressed in transplant biopsy tissues, before any overt clinical or histological manifestation of CR is detected in the transplanted subject.

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Intern Application No

PCT 03/09292

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, WPI Data, PAJ**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUTHANTHIRAN M: "Human renal allograft rejection: molecular characterization." NEPHROLOGY, DIALYSIS, TRANSPLANTATION: OFFICIAL PUBLICATION OF THE EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION - EUROPEAN RENAL ASSOCIATION. ENGLAND 1998, vol. 13 Suppl 1, 1998, pages 21-24, XP002267088 ISSN: 0931-0509 the whole document	1,5,6, 10,11
Y	----- -/-	2-4,7-9, 12-14

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 16 January 2004	Date of mailing of the international search report 27 05 2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Botz, J

BEST AVAILABLE COPY**INTERNATIONAL SEARCH REPORT**Intern Application No
PCT 03/09292**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHARMA V K ET AL: "Molecular correlates of human renal allograft rejection" TRANSPLANTATION PROCEEDINGS, vol. 30, no. 5, August 1998 (1998-08), pages 2364-2366, XP002267089 Meeting on New Dimensions in Transplantation: Weaving the Future; Florence, Italy; February 16-19, 1998 ISSN: 0041-1345 the whole document	1,5,6, 10,11
Y	-----	2-4,7-9, 12-14
X	TANG W H ET AL: "Activation of the serine proteinase system in chronic kidney rejection." TRANSPLANTATION. UNITED STATES 27 JUN 1998, vol. 65, no. 12, 27 June 1998 (1998-06-27), pages 1628-1634, XP008026499 ISSN: 0041-1337 the whole document	1,5,6, 10,11
Y	-----	2-4,7-9, 12-14
X	STREHLAU JURGEN ET AL: "Quantitative detection of immune activation transcripts as a diagnostic tool in kidney transplantation" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 2, 1997, pages 695-700, XP002267122 1997 ISSN: 0027-8424 the whole document	1,5,6, 10,11
Y	-----	2-4,7-9, 12-14
X	SUTHANTHIRAN MANIKKAM: "Clinical application of molecular biology: A study of allograft rejection with polymerase chain reaction" AMERICAN JOURNAL OF THE MEDICAL SCIENCES, vol. 313, no. 5, 1997, pages 264-267, XP008026444 ISSN: 0002-9629 page 264 - page 266; table 1	1,5,6, 10,11
Y	-----	2-4,7-9, 12-14
		-/-

BEST AVAILABLE COPY**INTERNATIONAL SEARCH REPORT**Inter Application No
PCT/ [REDACTED] 03/09292**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DELARUE FRANCOISE ET AL: "Prognostic value of plasminogen activator inhibitor type 1 mRNA in microdissected glomeruli from transplanted kidneys" TRANSPLANTATION (BALTIMORE), vol. 72, no. 7, 15 October 2001 (2001-10-15), pages 1256-1261, XP008026393 ISSN: 0041-1337 the whole document -----	1-14
Y	KAMOUN MALEK: "Cellular and molecular parameters in human renal allograft rejection" CLINICAL BIOCHEMISTRY, vol. 34, no. 1, February 2001 (2001-02), pages 29-34, XP001176799 ISSN: 0009-9120 page 30 - page 31 -----	1-14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09292

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14 (partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-4 are directed to a diagnostic methods / methods of treatment involving a surgical / sample taking step (biopsy) from the living human/animal body, practised on the human/animal body, the search has been carried out and based on the prognostic indication of CR in relationship to the candidate genes mentioned.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 (partially)

Invention number 1:

A method of early diagnosing chronic rejection (CR) in a transplanted subject, a method for monitoring CR in a transplanted subject at risk of developing CR, a method of preventing, inhibiting, reducing or treating CR in a transplanted subject in need of such treatment, a method for identifying agents for use in the prevention, inhibition, reduction or treatment of CR, all said methods above taking into consideration the mRNA expression of the first gene of table 1, namely the gene cytokeratin 15 / KRT15 with the GenBank accession number X07696 (c.f. page 19 of the description of the underlying application), the use of a gene or an expression product of a gene, namely the gene cytokeratin 15 / KRT15 with the GenBank accession number X07696 as an early biomarker for transplant rejection, and, finally, the use of a compound which modulates the synthesis, expression of activity of one or more genes as identified in Table 1, 2 or 3, in particular of the gene cytokeratin 15 / KRT15, or an expression product thereof, for the preparation of a medicament for prevention or treatment of CR in a transplanted subject;

2. claims: 1-14 (partially)

Inventions 2 - 33:

Idem for inventions 2 - 33, taking into consideration the mRNA expression levels of the genes mentioned in table 1 (from top to bottom);

3. claims: 1-14 (partially)

Inventions 34 - 65:

Idem for inventions 34 - 65, taking into consideration the mRNA expression levels of the genes mentioned in table 2 (from top to bottom);
